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| EXAMINER | |
|---|---|
| CHAKRABARTI, ARUN K | |
| **ART UNIT** | **PAPER NUMBER** |
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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/338,855 | Applicant(s) Sorge |
|---|---|---|
| | Examiner Arun Chakrabarti | Art Unit 1634 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Nov 18, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1, 3, 57-74, and 145-159* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3, 57-74, and 145-159* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

## DETAILED ACTION

### *Specification*

1. Claim 2 has been canceled without prejudice towards further prosecution and claims 1, 57, 69, and 159 have been amended.

#### Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 3, 150-153, 157 and 159 are rejected under 35 U.S.C. 103 (a) over Oefner et al. (U.S. Patent 5,795,976) (August 18, 1998) in view of Yin et al. (U.S. Patent 5,843,633) (December 1, 1998) further in view of Choo et al. (PCT International Publication Number WO 98/53060) (November 26, 1998).

Oefner et al. teach a method of enriching for and identifying a nucleic acid sequence difference with respect to a reference sequence and a method for accessing a sub-portion of a nucleic acid population (Abstract), comprising:

a) hybridizing a nucleic acid sample with a nucleic acid molecule comprising a sequence-specific binding activity under conditions which permit specific binding, wherein the sample comprises a subset of nucleic acid molecules having a sequence that binds to the sequence-specific binding activity, and wherein a bound subset of nucleic acid molecules is retained by the sequence-specific binding activity, such that the subset of bound nucleic acid molecules is enriched for molecules comprising the sequence recognized by the sequence specific binding activity (Column 9, lines 39-43, Example 2 and Column 13, line 21 to column 17, line 12 ); and

b) detecting a sequence difference with respect to a reference sequence in the subset of nucleic acid molecules (Column 18, lines 1-30 and Example 7, column 34, lines 7-13, Example 8, column 34, line 53 to column 36, line 27 and Figures 11A and 11B).

Oefner et al. teach a method wherein the molecule comprising sequence-specific binding activity is selected from nucleic acid molecules (Abstract, Column 22, line 59 to Column 24, line 58).

Oefner et al. teach a method wherein the sequence-specific binding activity is bound to a solid support (Examples 2, 3, 4, 5, 6 and 8 and Figures 1-4 and 6-13).

Oefner et al. teach a method of enriching for and identifying a nucleic acid sequence difference with respect to a reference sequence (Abstract), comprising:

a) fragmenting a nucleic acid sample from one or more individuals (Column 9, lines 39-43);

b) physically separating a subset of the nucleic acid fragments based on the size of the fragments (Example 2 and Column 13, line 21 to column 17, line 12);

c) operatively linking the subset of step (b) with molecules capable of being replicated (Column 13, line 21 to column 17, line 12);

d) introducing the linked subset of molecules of step c) into a system capable of replicating the linked subset of molecules, and replicating the subset of linked molecules to form an enriched collection of replicated molecules (Column 17, lines 14-67).

e) detecting one or more nucleotide sequence differences in the members of the collection of step (d) with a method capable of detecting one or more nucleotide differences with respect to a reference sequence (Column 18, lines 1-30 and Example 7, column 34, lines 7-13, Example 8, column 34, line 53 to column 36, line 27 and Figures 11A and 11B).

Oefner et al. teach a method wherein the system capable of replicating the linked molecules comprises host cells and the collection of replicated molecules comprises a library (Column 22, line 59 to Column 24, line 58).

Oefner et al. teach a method wherein the system capable of detecting one or more nucleotide conformational differences comprises DNA sequencing by electrophoresis (Column 35, lines 3-27).

Oefner et al. teach a method wherein the method capable of detecting one or more nucleotide difference comprises denaturing HPLC (Examples 2, 3, 4, 5, 6 and 8 and Figures 1-4 and 6-13).

Oefner et al. teach a method wherein the method capable of detecting one or more nucleotide difference comprises a protein capable of detecting mismatches between duplexed strands of nucleic acid (Column 23, lines 45-56).

Oefner et al. teach a method wherein the steps (a)- (b) are repeated one or more times to increase the enrichment of the enriched collection of repeated molecules (Example 7).

Although Oefner et al may not teach the exact same order of carrying out the steps of the claimed invention, it is prima facie obvious to carry out the steps in a little bit modified order since MPEP 2144.04 further states, " *In re Gibson,* 39 F.2d 975, 5 USPQ 230 (CCPA 1930) Selection of any order of mixing ingredients is *prima facie* obvious".

Oefner et al do not teach a method wherein a subset of nucleic acid molecules having a sequence that binds to the sequence-specific binding activity comprises less than every molecule in the population of nucleic acid molecules in the sample.

Yin et al. teach a method wherein a subset of nucleic acid molecules having a sequence that binds to the sequence-specific binding activity comprises less than every molecule in the population of nucleic acid molecules in the sample (Column 9, lines 31-47).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine within the method of comparative hybridization and sequencing of Oefner et al., the method wherein a subset of nucleic acid molecules having a sequence that binds to the sequence-specific binding activity comprises less than every molecule in the population of nucleic acid molecules in the sample of Yin et al. since Yin et al state, "Sequence similarity is calculated based on a reference sequence, which may be a subset of a larger sequence, such as conserved motif, coding region, flanking region, etc. (Column 9, lines 37-39)". An ordinary artisan would have been motivated by the express statement of Yin et al to substitute and combine within the method of comparative hybridization and sequencing of Oefner et al., the method wherein a subset of nucleic acid molecules having a sequence that binds to the sequence-specific binding activity comprises less than every molecule in the population of nucleic acid molecules in the sample of Yin et al. in order to achieve the express advantages, as noted by Yin et al. , of a method which provides sequence similarity calculation based on a reference sequence, which may be a subset of a larger sequence, such as conserved motif, coding region, flanking region, etc.

Oefner et al. in view of Yin et al do not teach the method of contacting a nucleic acid sample with a molecule comprising a sequence-specific binding activity selected from

transcription factors or proteins with zinc-finger DNA binding domains, which recognize DNA having a particular G+C content or methylation status.

Choo et al teach the method of contacting a nucleic acid sample with a molecule comprising a sequence-specific binding activity selected from transcription factors or proteins with zinc-finger DNA binding domains, which recognize DNA having a particular G+C content or methylation status (Abstract, and Claims 1-21, and Page 11, lines 5 to 29 and Examples 1-5).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine within the method of comparative hybridization and sequencing of Oefner et al. in view of Yin et al., the method of contacting a nucleic acid sample with a molecule comprising a sequence-specific binding activity selected from transcription factors or proteins with zinc-finger DNA binding domains, which recognize DNA having a particular G+C content or methylation status of Choo et al. since Choo et al state, "The present invention provides a more complete code which permits the selection of any nucleic acid sequence as the target sequence, and the design of a specific nucleic acid binding protein which will bind thereto. Moreover, the invention provides a method by which a zinc finger protein specific for any given nucleic acid sequence may be designed and optimized. The present invention therefore concerns a recognition code which has been elucidated for the interactions of classical zinc fingers with nucleic acid. In this case a pattern of rules is provided which covers binding to all nucleic acid sequences (Page 2, line 25 to page 3, line 2)". An ordinary artisan would have been motivated by the express statement of Yin et al to substitute and combine

within the method of comparative hybridization and sequencing of Oefner et al. in view of Yin et al., the method of contacting a nucleic acid sample with a molecule comprising a sequence-specific binding activity selected from transcription factors or proteins with zinc-finger DNA binding domains, which recognize DNA having a particular G+C content or methylation status of Choo et al. in order to achieve the express advantages, as noted by Choo et al., of an invention which provides a more complete code which permits the selection of any nucleic acid sequence as the target sequence, and the design of a specific nucleic acid binding protein which will bind thereto and which also provides a method by which a zinc finger protein specific for any given nucleic acid sequence may be designed and optimized and which concerns a recognition code which has been elucidated for the interactions of classical zinc fingers with nucleic acid and which provides a pattern of rules that covers binding to all nucleic acid sequences.

4. Claims 1-3, 57-68, 145-153, 157 and 159 are rejected under 35 U.S.C. 103 (a) over Oefner et al. (U.S. Patent 5,795,976) (August 18, 1998) in view of Yin et al. (U.S. Patent 5,843,633) (December 1, 1998) further in view of Choo et al. (PCT International Publication Number WO 98/53060) (November 26, 1998) further in view of Gaitanaris (U.S. Patent 6,228,939 B1) (May 8, 2001).

Oefner et al in view of Yin et al further in view of Choo et al. teach the method of claims 1-3, 150-153, 157 and 159 as described above.

Oefner et al in view of Yin et al further in view of Choo et al. do not teach the method, wherein a nucleic acid fragment is operatively linked to a vector and replicating the operatively linked subset to form an enriched collection of replicated molecules.

Gaitanaris teach the method, wherein a nucleic acid fragment is operatively linked to a vector and replicating the operatively linked subset to form an enriched collection of replicated molecules (Column 3, lines 43-58 and Column 15, line 23 to column 16, line 10).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine within the method of comparative hybridization and sequencing of Oefner et al in view of Yin et al further in view of Choo et al., the method, wherein a nucleic acid fragment is operatively linked to a vector and replicating the operatively linked subset to form an enriched collection of replicated molecules of Gaitanaris since Gaitanaris states, "The invention features a method for identifying a mutagenized mammalian gene (Column 3, lines 43-44)". An ordinary artisan would have been motivated by the express statement of Gaitanaris to substitute and combine within the method of comparative hybridization and sequencing of Oefner et al in view of Yin et al further in view of Choo et al., the method wherein a nucleic acid fragment is operatively linked to a vector and replicating the operatively linked subset to form an enriched collection of replicated molecules of Gaitanaris in order to achieve the express advantages, as noted by Gaitanaris, of an invention that features a method for identifying a mutagenized mammalian gene.

5. Claims 1-3, 69-74, and 150-159 are rejected under 35 U.S.C. 103 (a) over Oefner et al. (U.S. Patent 5,795,976) (August 18, 1998) in view of Yin et al. (U.S. Patent 5,843,633) (December 1, 1998)further in view of Choo et al. (PCT International Publication Number WO 98/53060) (November 26, 1998) further in view of Cabib et al. (U.S. Patent 5,912,165) (June 15, 1999).

Oefner et al in view of Yin et al further in view of Choo et al. teach the method of claims 1-3, 150-153, 157 and 159 as described above.

Oefner et al in view of Yin et al further in view of Choo et al. do not teach the fragmenting a nucleic acid sample by endonuclease digestion.

Cabib et al teach the fragmenting a nucleic acid sample by restriction endonuclease digestion (Example 6, column 41, lines 4-26).

Cabib et al teach the fragmenting a nucleic acid sample with one or more sequence - specific cleavage agents restriction endonuclease to produce nucleic acid fragments (Example 6, column 41, lines 4-26). Cabib et al teach the method wherein at least one restriction endonuclease cleaves DNA infrequently (Example 6, column 41, lines 21-23).

Oefner et al in view of Yin et al further in view of Choo et al. do not teach the method wherein the infrequently cleaving restriction endonuclease is selected from NotI.

Cabib et al teach the method wherein the infrequently cleaving restriction endonuclease is selected from NotI (Column 41, lines 21-26).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine within the method of comparative hybridization and sequencing of Oefner et al in view of Yin et al further in view of Choo et al., the method of NotI restriction endonuclease digestion of Cabib et al. since Cabib et al state, "A complete digestion by a rare cutter endonuclease (e.g. NotI) is used. The latter is presently preferred, since a complete digestion can be repeated to yield identical results in independent trials, whereas partial digestion is random in nature (Column 41, lines 22-26)". An ordinary artisan would have been motivated by the express statement of Cabib et al to substitute and combine within the method of comparative hybridization and sequencing of Oefner et al in view of Yin et al further in view of Choo et al., the method of NotI restriction endonuclease digestion of Cabib et al., in order to achieve the express advantages, as noted by Cabib et al. , of a rare cutter restriction endonuclease (e.g. NotI) which provides a complete digestion and which is presently preferred, since a complete digestion can be repeated to yield identical results in independent trials, whereas partial digestion is random in nature.

***Response to Amendment***

6. In response to amendment, previous 112 (second paragraph) and 103 (a) rejections are withdrawn. However, three new 103 rejections are hereby being included.

***Response to Arguments***

7. Applicant's arguments with respect to claim 1 and all pending claims dependent on claim 1, have been considered but are moot in view of the new ground(s) of rejection.

Applicant also argues that rejection of claim 157 should be withdrawn because none of the cited references teaches a restriction endonuclease that cleaves the nucleic acid sample 300,000 times or fewer. This argument is not persuasive. Oefner et al clearly teaches a restriction endonuclease that cleaves the nucleic acid sample 300,000 times or fewer (Column 3, lines 43-61).

Moreover, applicant requested an explanation how the motivation statement of Yin et al. cited in the last office action provides the basis of 103(a) rejection. In response, applicant is hereby notified that Yin et al. teach a method wherein a subset of nucleic acid molecules having a sequence that binds to the sequence-specific binding activity comprises less than every molecule in the population of nucleic acid molecules in the sample (Column 9, lines 31-47). Yin et al provides motivation as Yin et al state, "Sequence similarity is calculated based on a reference sequence, which may be a subset of a larger sequence, such as conserved motif, coding region, flanking region, etc. (Column 9, lines 37-39)". In response to applicant's argument that Yin et al has a different motivation, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

***Conclusion***

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti , Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401. Any inquiry of a general nature or relating to the status of this

application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti,

Patent Examiner,

December 6, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600